Evaluating the Efficacy of Biomarkers in the Diagnosis and Treatment of Gyneacological Malignancies: A Review

Omozuwa ES[1], Atoe K[2]*

[1]Department of Obstetrics and Gynaecology, Edo State University Uzairue, Edo State, Nigeria
[2]Department of Chemical Pathology, Edo State University Uzairue, Edo State, Nigeria

***Corresponding author**: atoe.kenneth@edouniversity.edu.ng

ABSTRACT

The current review examines the pivotal role of biomarkers in the diagnosis and treatment of gynaecological cancers, with emphasis on ovarian cancer. It explores how biomarkers such as CA125 and HE4 are used to predict disease onset, detect subclinical illness, and assess treatment responses, especially in the context of ovarian cancer recurrence. The review also addresses the challenges inherent in early detection and management of gynaecological cancers, highlighting the asymptomatic nature and high mortality rate associated with ovarian cancer. It underscores the potential of biomarkers to significantly enhance early detection and treatment strategies, thereby improving patient outcomes. Additionally, this review discusses the relevance of biomarkers across various gynaecological cancers, including cervical, endometrial, and vulvar malignancies, outlining associated risk factors and treatment options. Finally, the review emphasizes the need for further research to validate and integrate effective biomarkers into clinical practice, with the aim of advancing the management of gynaecological cancers.

Keywords*:* Malignancies, Biomarker, Chemotherapy, Reproduction, Cervix, Endometrium

.

INTRODUCTION

In 1989, an identifiable and quantifiable biological variable used to measure individual well-being and physiology in the context of illness risk as well as detection was identified, leading to the coining of the word "biomarker" (derived from "biological marker").[1] A feature that is scientifically assessed as well as examined potentially, a marker of regular biological methods, pathological procedures, or pharmaceutical reactions towards treatment" is the description of a biomarker given by the National Institutes of Health in 2001.[2] The World Health Organization (WHO) defined a biomarker as any material, procedure, or architecture which may be assessed through human body or its byproducts and influences or forecasts the development of an outcome or illness.[3] Biomarkers have multiple applications, including as "antecedent biomarkers" that anticipate the beginning of a medical condition in the future, “examining biomarkers” that detect subclinical illness, “diagnosing biomarkers” that recognize technically exhibited illness, “staging biomarkers” that define the impact of a disease, “prognostic and therapeutic biomarkers” that gauge the course of an illness along with its response to therapy, and acceptance or rejection as well as results requirements in clinical studies.[1] While a number of characteristics such as genetic variations, functional testing, radiological results, and signals, can be classified as "biomarkers," the key point of this review is to evaluate how well biomarkers work in the detection and management of gynaecological cancers.

Significance of Biomarkers in Gynaecological Malignancies

A biomarker's accuracy is determined by its inability to be detected in healthy people, while its efficacy is determined by how well it identifies patients illness based on the presence of the biomarker.[4] False-positive results or negative findings will result from a biomarker that possesses only one of these characteristics.[4] Current researches are focused on how serum biomarkers relate to the prognosis of ovarian cancer resurgence. In this sense, biomarkers are regarded as prognostic signals that classify patients into varying risk categories for a particular event and provides a projection for the condition's reappearance.[5] Nowadays, the main malignancy biomarker commonly used in routine medical practice for monitoring disease is blood CA125, which is employed in detecting clinical signs of recurrence.[6] The outcome of care corresponds to CA125 level, which have been shown to increase by 4.8% months prior to clinical disease recurrence,[7] a period within which various types of traditional treatments are usually explored. A recent study has demonstrated the significant benefits of early treatments.[8] Finding a suitable biomarkers that could identify ovarian cancer resurgence well in advance of the rise in blood CA125 level is important in allowing patients to benefit from proactive therapy, which aims to prolong the free-from-illness period and improve the quality of life. Many biomarkers, such as HE4, osteopontin (OPN), mesothelin (MSLN), folate receptor α (FOLR1), paraneoplastic antigens, miRNA, cancer stem cells (CSCs), as well as various combinations of these

biomarkers, are being examined by scientists to determine their efficacy as predictive indicators of ovarian cancer incident.

To determine the possible significance of biomarkers in the early detection of ovarian cancer, this review examined currently accessible studies. This review attempts to examine the function of biomarkers in the early stage of ovarian cancer incidence. The review also attempts to address the understanding of gynaecological malignancies, diagnostic and treatment challenges, the significance of biomarkers, and their effectiveness in diagnosis and treatment strategies, the risk factors and aetiology of gynaecological cancers including Li-Fraumeni syndrome, Lynch syndrome, familial adenomatous polyposis, and hereditary breast and ovarian cancer syndrome. It also discusses the complexities associated with the early detection and management of gynaecological cancers, with a particular focus on ovarian cancer due to its asymptomatic nature and high mortality rate. The review laid the foundation for a thorough investigation of how biomarkers could improve the detection and management of gynecological cancers.

Understanding Gynaecological Malignancies

Ovarian Cancers

Majority of ovarian tumours commonly present as benign growth and occurred under the age of 40 years, while the advanced malignant types are found above the age of 40 and 50 years. There are several sub-types; mature teratoma, serous cystadenoma and mucinous cystadenoma are the commonly presented benign ones while serous cystadenocarcinoma is an example of malignant tumour especially when they are bilateral.[9-11] Among the deadly cancers in the human body, ovarian cancer is classify as the fifth most lethal tumour in females after lung, colo-rectal, breast, as well as pancreatic cancers.

In the female genital organs, ovarian malignancy is the most common type of female genital cancers after cervical cancer and statistically among the top ten common cancers occurring globally. There is a higher death rate due to ovarian cancer than cervical and uterine cancers put together with a poor five-year survival rate. Ovarian cancers are the most common female genital cancer in Nigeria and ranks seventh in the new cases of cancer in Nigeria in 2018; ranks 2.9% of all cancer deaths in Nigeria.[12,13] Lifetime risk of ovarian cancer is 0.42% in Nigeria with age specific incidence rate of 4.4/100,000 in Nigeria and 6.6/100000 globally. Age specific morality rate is 3.6/100,000 in Nigeria and 3.9/100000 worldwide and the incidence is increasing in the country and about 85% present as stage III/IV.[14]

The management of advanced ovarian cancers is multi-disciplinary and a staging laparotomy is required to properly stage the disease. Current treatment modalities are cytoreductive or radical debulking surgeries, chemotherapy and radiotherapy. Diagnosis and monitoring using CA125 and assessment for risk of malignancy index help in early involvement of a gynaecologic oncologist for optimal care. Strategies available for early detection of ovarian malignancies includes transvaginal

ultrasonography (TVS), tumour markers CA125, HEA4, multimodal screening (MMS), genetic risk and symptoms base screening. A 5-year survival rate is higher for ovarian cancers treated at early stage of the disease. Measures currently available for ovarian cancers reduction involve the use of the above mentioned methods, and early detection and treatment. Risk reduction bilateral salpingo-oophorectomy for ladies having strong family history of ovarian cancer, Breast Cancer 1 and Breast Cancer 2 (BRCA1 and BRCA2) mutation. When undergoing gynaecologic treatment on suspicious ovaries, it is important to prophylactically remove each fallopian tubes in those at high risk.

By avoiding tumors which develop within the fallopian tubes, excision of both tubes during the procedure of hysterectomy or opportunistic salpingectomy helps reduce the incidence of ovarian cancer. Giving the available information, females who have a lower than 5% chance of developing ovarian cancer should be offered salpingectomy alone. [13,14]

Other Types of Gynaecological Malignancies

1. Cervical Malignancies

Cervical cancer which is the most common cancer in women worldwide affects over half a million women annually. Over 250 million deaths result from the cancer every year. Approximately 94% out of the three hundred thousand (300,000) cervical cancer related fatalities in 2022 occurred in low and middle income nations. Sub-Sahara Africa and Central America are regions in the world with highest incidence and death from cervical cancers.[14] The burden created by cervical malignancies are huge among countries. However disparity exist among the regions as a result of inaccessibility to vaccine, treatment services, the risk factors that cause limitation including HIV prevalence, economic factors such as gender biases, sex as well as poverty.[14] Poor socioeconomic status, intravenous drug use and multiple sexual partners predispose women to HIV acquisition which greatly increase the chances of developing cervical cancer. Women who are HIV sero-positive have the chance of developing cervical cancer in contrast to population without HIV infection, and studies have shown that five percent of all cervical cancer cases are due to HIV. [13,14] Other risk factors for cervical cancer includes early sexual debut, poor immunity, family history and heredity, multi-parity, smoking and exposure to radiations.

Most cases of cervical cancer are attributed to human papillomavirus which is a sexually transmitted infection. Researches have shown that for abnormal cells to become cancerous, it takes about 15 – 20 years. However, woman with weakened immune systems, such as those who are HIV positive, the process can be faster which is about 5–10 years. Cervical cancer development cannot occur unless there is the presence of certain attributes which are the risk factors mentioned earlier such as the level of oncognenicity in human papillomavirus, level of immune system, and other sexually transmitted diseases, etc.[14,15]

Early detection and treatment remain the cornerstone in the fight against cervical cancers. Screening entails periodic pap smear from the age of 30 years. The key to prevent

and manage cervical cancer is to encourage public awareness and ability to access information as well as services. Highly effective way to prevent cervical cancer is to vaccinate all girls at the age of nine to fourteen years.[15] Six diverse kinds of HPV vaccines are currently available globally. All are safe and protect against high oncogenic HPV types 16 and 18, which are responsible for cervical cancers.[14]

2. Endometrial Malignancies

Endometrial cancer (EC) manifest majorly in the 6th decade of life, especially among women of low parity. Other related risk factors associated with cancer of the endometrium include race, smoking, family history and exposure to carcinogens. It ranks the 6th most prevalence cancer in women globally, with over 400,000 new cases reported in 2020.[15] Another rare form of tumour that can arise from the uterus is uterine sarcoma. This cancer is usually diagnosed at an early stage because it occurred with irregular vaginal discharge and definitive surgical removal of the uterus is currently the mainstay of management. Endometrial cancers also commonly present with postmenopausal bleeding and pelvic pains. Other current management options include molecular characterization and risk assessment and treatment based on data gathering. For advanced and recurrent disease, management relied heavily on combination chemotherapy with platinum based therapy.

Other medical options for the treatment of patients with endometrial cancer include incorporation of check point blockers, for example patients who are suffering from microsatellite instability of lack of mismatch repair tumours as well as combination with lenvatinib.[16] The growing prevalence of obesity and ageing population have contributed to the increased incidence and death rate. Researchers found that endometrial cancer has strong association with obesity in comparison with other malignancies.[17,18]

3. Gestational Trophoblastic Disease (GTD)

A range of trophoblastic cancers connected to pregnancy and childbirth is known as gestational trophoblastic disease (GTD). GTD is divided cytopathologically into; cancerous aggressive mole, complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), epithelioid trophoblastic tumor (ETT), placental site trophoblastic tumor (PSTT), and choriocarcinoma. The invasive forms are called gestational trophoblastic neoplasia (GTN). Many different forms of GTD produce human chorionic gonadotrophin (hCG) as a biomarker which is used for diagnosis and treatment monitoring.[19]

Based on research findings, the Asian continent, the Arabian Peninsula, and Africa have the greatest risk of GTD. Among the North Americans, the estimated frequency of choriocarcinoma increases by one in every forty thousand pregnancies, whereas the prevalence of hydatidiform mole is about 0.57 - 2 in every thousand pregnancies. In Southeast Europe and Asia, it amounts to 9.2 and 3.3 in every forty thousand pregnancies in these regions, respectively.[20,21]

Patients typically present with vaginal bleeding during the second trimester and

passage of grape-like vesicles with sometimes uterine size larger than due date. Ultrasound examination during the first trimester is frequently used to diagnose GTD. Hyperemesis gravidarum, preeclampsia, along with hyperthyroidism are widespread in the first trimester and vesicles can be visible when the gestational product passes vaginally.[22,23]

4. Vulva Malignancies

Vulval cancer is an uncommon malignancy that primarily affects older women. Approximately 4% of all gynaecological cancers are vulval cancer. Vulval cancer frequently manifested as a sore lump, ulcer, or itching; at a more severe stage, large fungating ulcers including distant metastases are seen. The management of vulval cancer is interdisciplinary and tailored to each patient. Regarding initial disease, extensive localization of the lesion is advised, typically alongside surgical screening of the pelvic nodes via multiple operations.[9,11] Management of advanced localized vulval tumors is intricate but extremely customized; it may involve radical removal followed by the rebuilding process.

Nowadays, surveillance lymph node evaluation with staging has replaced en-bloc as the typical treatment. Assuming a surveillance node biopsy yields unsuccessful findings, these patients do not undergo groin dissection or inguinofemoral lymphadenectomy during surgical grading. According to the results of the recent GROINSS-VII research, radiation is a safe substitute for surgery for patients having sentinel lymph node micro metastases (≤ 2 mm) who also have reduced treatment-related complication as well as a diminished groin return risk.[24] Vulva cancers present in different ways depending on cell types and the structures involved. The most common subtype is called squamous cell carcinoma. They account for 75-90% of all primary cancers of the vulva and majority of vulva cancer mortalities are from high grade lesions.[24,25] Squamous cell carcinoma of the vulva is a malignant growth with high propensity for distant spread. Early spread is usually detected by sentinel node mapping and other advanced imaging techniques following presentation. Commonly in our environment, ignorance, financial constraints, fear of cancer, lack of health care facility, fear of surgery and chemoradiation, and superstitious traditional beliefs are reasons for late presentation in advanced stage of the disease.[24] The risk factors for acquiring vulva cancer include increasing age especially in postmenopausal period, exposure to human papiliomavirus (HPV) which is sexually transmitted as a result of multiple sexual partners. Others are smoking, weakened immune system and previous history of precancerous condition of the vulva. Presentation in the postmenopausal period is often of the malignant variant in our environment. Postmenopausal women in their fifth and sixth decades are at a higher risk of advanced cancer of the vulva and other genital malignancies as such this group of patients should be approached cautiously.[14,15,17]

5. Vaginal Malignancies

Vaginal malignancy accounts for 1-2% of tumours that are malignant, that affect the

female genitals, and are among the most uncommon gynecological malignancies. The vast majority affected females have squamous cell carcinoma. Tobacco use, urinary tract dysplasia and HPV contact are associated with increased risk of vaginal cancer. While vaginal cancer is prevalent in women older than 60 years, genital adenocarcinomas mostly develop in younger women, especially in cases where the woman was exposed to DES in utero, which is currently very rare. It is actually more frequent for secondary vaginal cancer to develop through metastasis worldwide, such as the cervix (30 percent of occurrences), endometrial (20 percent), colon/rectum (ten percent), ovary (five percent) or vulva (five percent) compared to initial cancer of the vagina.[26]

Causes of Gynaecological Cancers

1. **Hereditary Breast and Ovarian Cancer Syndrome**

The cancer that is most likely to affect a woman is cancer of the breast. According to the World Health Organization (WHO), more than two million new cases of breast cancer were recorded in 2018, accounting for 11.6% of all newly diagnosed cases of cancer in both men and women. The total chance of breast cancer between the ages of 0 and 74 years was 2.81–4.17% in Asia, 9.32% in the US and Canada, and 10.16% in the Pacific Islands along with Australia. This implies that breast cancer is a type of disease that is widespread and impacts a large number of people.

Moreover, 5–10% of people with breast cancer have a hereditary predisposition to the disease. In addition to determining cancer susceptibility, researches on hereditary breast and ovarian cancer (HBOC) includes evaluation of the implementation of family preventive measures, risk assessment, cancer prevention strategies, and contemporary breast cancer medicines.

According to studies, a syndrome called Familial Breast Cancer (FBC) affects approximately fifteen percent of those with breast cancer who have a documented family history of multiple female breast or ovarian cancer tumors.[8] People that are genetically predisposed to cancer are contained in FBC. HBOC indicates genetic cancer of the breast and ovary. The National Cancer Institute defines the condition as "a genetic condition in which the possibility involving malignancies in the breast (especially before approaching the average age of 50) in addition to malignancy that affects the uterus increases than normal." Specific BRCA1 or BRCA2 abnormalities are the primary aetiology of the majority of HBOC syndrome. In addition to prostate, pancreatic, and melanoma cancers, those with HBOC could also be more susceptible to other malignancies.[9]

2. **Lynch Syndrome**

Lynch Syndrome (LS) is a genetic disorder characterized by structural pathogenic alteration affecting part of the mismatch repair (MMR) gene. Moreover, LS may result from removals of the EPCAM gene, which normalizes MSH2 gene expression. Colon cancer, upper gastrointestinal (GI) tract malignancies, urinary cancers, skin cancers, and other cancers that afflict both men and women are among the many cancers to which

individuals are predisposed by this autosomal dominant syndrome. Endometrial and ovarian cancers are more common in women with LS, whereas prostate cancer is more common in males with LS. Importantly, malignancies connected to LS frequently appear at younger ages, below the national screening standards, which affects the life expectancy adjustments that are gained via early detection and preventative measures.[11,13]

Several interventions significantly improve outcomes for individuals with LS, focusing on cancer prevention and early detection. These interventions include regular colonoscopies, chemoprophylaxis, and preventive gynecological surgeries. Based on the particular MMR gene pathogenic variation, there are differences in lifelong risk of acquiring cancer. For instance, individuals with an MLH1 variant are at a lifetime CRC risk of 44–53%, with some studies indicating up to 70%. For MSH2 carriers, the risk ranges from 42–46%, while for MSH6 carriers, it is about 18–20%, and for PMS2 carriers, it is the lowest at approximately 10–13%. Therefore, clinical management strategies must consider the gene-specific risk profile of each individual to optimize prevention and early detection efforts.[14]

3. Familial Adenomatous Polyposis

Hundreds to thousands of colorectal adenomatous polyps, which usually appear around the beginning of puberty and persist throughout the life span, is the hallmark of familial adenomatous polyposis (FAP), which is characterized as an autosomal dominant pattern of inheritance. By the time an individual reaches age 50 years, colon cancer nearly always results from FAP if treatment is not received.[15] FAP affects both genders equally and has a rate of 2.29 to 3.2 cases per million patients. It accounts for between 0.5% and 1% of all instances of colorectal cancer.[17] The first histological account of adenomatous polyposis was published in 1881 by Sklifasowski, who reported on a fifty-one year old merchant who had seven years of bloody diarrhea alongside stomach pains. Big polyps were surgically eliminated, and histological analysis revealed that they were adenomas. Less than 100 colonic adenomas are involved in attenuated familial adenomatous polyposis (aFAP), a subtype of familial adenomatous polyposis that usually affects people over 40 years. With its later-onset adenomas, which are frequently manageable endoscopically, this milder phenotype permits a considerable delay in surgery.[18]

4. Li-Fraumeni Syndrome

Frederick Li and Joseph Fraumeni initially used the term Li-Fraumeni disorder (LFD) in 1969.[16] It is said to be the "custodian of the genome," the tumour protein, p53 tumour suppressor protein has a germline mutation that causes Li-Fraumeni Syndrome (LFS) a disease predisposed to cancer.[19] The mutation leads to dysplasia and neoplasia, resulting in breakdown of cellular stability.[20] Individuals with LFS develop multiple primary cancers throughout their lifetime, which can manifest as cancers that are metachronous or concurrent. The condition is relatively rare, with germline TP53 mutations which is estimated at roughly 1 in 5000 individuals, or

0.02 percent. LFS commonly exhibits familial inheritance with an autosomal-dominant pattern, linked to TP53 mutations on chromosome 17p13. In familial cases, incomplete penetrance is observed in female carriers with 90 to 100% and 70–75% which occur in male carriers. LFS acquired from spontaneous mutations is much less common, affecting only about 7–20% of LFS patients who acquire it through de novo mutations.[19] Clinically, patients who possess LFS may present with a range of cancers across various tissues. Though, certain tissues are more susceptible due to their robust apoptosis during development, leading to a narrower spectrum of characteristic tumours associated with the syndrome. Recognizing tumours from this spectrum can raise suspicion for LFS, prompting clinicians to consider genetic testing and surveillance for new cancers in affected individuals.[21]

Current Diagnostic and Treatment Challenges

The high incidence and fatality rates of gynecological malignancies persist, making them a serious concern.[27] To address these challenges, various protocols aim to reduce the occurrence and impact of these cancers have been formulated. Cancer management typically involves three key steps which include primary, secondary, and tertiary prevention. Changing one's lifestyle, being vaccinated, and receiving preventive treatments are the main methods of primary prevention. Secondary prevention, which is commonly accomplished through early detection screening programs, is identifying and treating the illness before it presents clinically. Controlling ongoing chronic diseases is the aim for further management effort to avert negative effects or irreversible damage.[25] In spite of considerable research awareness and advancements toward prevention and therapy, the prognosis for gynecological cancers remains poor. Prevention and early detection strategies may not always be applicable, particularly in the case of ovarian and endometrial cancers. Current screening tests are not highly effective for detecting these cancers at early stages.[24]

Cervical cancer, especially prevalent in developing countries, poses a significant health burden and is a major factor in cancer-related mortality in women. Primary prevention efforts primarily revolve around the Human Papillomavirus (HPV) vaccine, which reduces the chance of developing Human Papillomavirus infection, precancerous lesions, as well as incidence of cervical cancer.[26,29] Unlike cancer of the cervix, there is certainly not recommended screening for endometrial cancer due to current clinical guidelines. However, promoting a healthy lifestyle and balanced diet is advised due to well-established risk factors such as metabolic syndrome, obesity, and diabetes. Despite the absence of a specific screening programme, the majority of endometrial cancer cases had an early diagnosis.[30] Ovarian cancer presents a unique challenge as there are no structured prevention programmes or effective screening tests. Diagnosis is often delayed due to the asymptomatic nature of the disease until it reaches an advanced stage, leading to poor prognosis. High-risk women with genetic

mutations (e.g., BRCA mutations) or family syndromes associated with ovarian cancer may undergo surveillance and prophylactic treatment programs to mitigate risks. However, the high mortality rate underscores the need for improved strategies in detection and management.[31]

Role of Biomarkers in Gynealogical Malignancies

Numerous biomarkers have been explored for cervical cancer (CC) screening and assessing post-treatment recurrence risk. However, their ability to accurately predict prognosis remains debated.[32] More reliable indicators are still being sought after for CC early diagnosis and prognostic surveillance. Serum tumor biomarkers have become important instruments in the control of cancer, helping in prognosis, testing, treatment, and evaluation of therapy response.[33] Biomarkers play a pivotal role in managing gynaecological malignancies, providing crucial insights for optimal treatment decisions, particularly in advanced-stage cases. Small extracellular vesicles, or exosomes, having a diameter of 30 to 150 nm have garnered attention for their involvement in intercellular communication and potential as diagnostic and prognostic indicators. Exosomes serve as vehicles for cargo uptake, transport, and release, influencing the pathogenesis, diagnosis, treatment, and prognosis of gynaecological cancers.[34]

Liquid biopsy techniques utilizing exosomes offer noninvasive and personalized approaches for evaluating cancer status. In ovarian cancer, exosomes are implicated in disease progression, metastasis, drug resistance, and treatment response, presenting opportunities for diagnostic marker development. Similarly, exosomes play significant roles in cervical and endometrial cancers, impacting disease pathogenesis, management, and treatment outcomes.[34] Understanding the functions of exosomes in these contexts enhances the ability to address and manage gynecological malignancies effectively.

Biomarkers in Gynaecological Malignancies

Identification and Classification of Biomarkers

Biomarkers, crucial indicators in disease identification, progression, and clinical outcomes, are classified in various ways. Understanding these classifications is essential for their effective use in healthcare.[35] Using techniques from molecular science as well as inheritance; a single classification approach divides biomarkers into three groups. Natural history biomarkers, sometimes referred to as type 0 biomarkers, track the course of a disease and have a correlation with known clinical variables. Serum creatinine levels, for example, can be used as type 0 biomarkers to evaluate renal damage or function.[36] Type 1 Biomarkers: These biomarkers gauge the activity of drugs and can be further categorized into efficacy, mechanism, and toxicity biomarkers. In autoimmune disorders such as rheumatoid arthritis, cytokines function as mechanism biomarkers, whereas blood sugar levels are utilized to serve as an efficacy biomarker to track the result of insulin treatment.[37] Biomarkers of Type II Clinical

illness outcomes are replaced with surrogate indicators, also known as surrogate endpoints, which also forecast the results of therapeutic treatments. Cholesterol levels in heart disease, though correlated with increased risk, may not always manifest consistently, exemplifying type 2 biomarkers' complexity. Another classification scheme divides biomarkers into four classes: Prognostic Biomarkers: These indicators predict the prognosis of an illness in people who are not receiving treatment. For instance, reduced rates of disease-free survival are predicted in Human Epidermal Growth Factor Receptor 2 positive metastatic breast cancer based on the PIK3CA mutation status.[38] Projecting Biomarkers Targeted psychotherapy is made possible through prognostic indicators, which identifies individuals deemed more probable to benefit from a specific treatment. One biomarker potentially is capable of being used for estimating the efficacy of erlotinib therapy is the existence of EGFR variants in progressive non-small-cell lung cancers.

Drug-drug interaction biomarkers: By evaluating the pharmacological effects of medications, these indicators determine if treatment is having the expected impact. The levels of phosphorylated AKT (pAKT) are used as pharmacodynamic biomarkers to verify the effectiveness of Phosphoinositide 3-kinase inhibitors in the treatment of cancer.[39] Surrogate End-point Biomarkers: Similar to type 2 biomarkers, surrogate end-points substitute for clinical outcomes. Surrogate biomarkers like blood pressure for cardiac disease should effectively predict clinical outcomes to be useful in treatment evaluation. Additionally, indicators of exposure and disease may be distinguished; the former helps forecast risk, while the latter aids in diagnosis and disease monitoring. Additionally, biomarkers are capable of being categorized as being related to drugs or diseases, allowing medical professionals to employ more targeted treatment techniques.[40]

Biomarker Testing Methods and Technologies

A reliable, economical, and effective tool for prediction, diagnosis, and tracking illness resurgence is what biomarker detection researchers want to develop. By monitoring the decrease in their concentration, biomarkers also help with therapy examination. A number of techniques that depend on extremely exact identification of biomarkers have achieved significant advancements in biomarker detection technology. These consist of mass-sensing BioCD peptide array, gel electrophoresis, surface plasmon resonance (SPR), substrate improved Raman analysis (SERS), colorimetric testing, galvanic test, along with brightness techniques. Elsewhere they are used in diagnostics to enhance treatment. Conventional immunoassays, that utilize an indicator antibodies enabling experiment read-out along with a capture antibody attached to solid backing enabling concentrate gathering, are the principles of many of these techniques. However, a common issue they deal with involves the general adhesion of non-target peptides across the biosensor interface. Because of this, existing methods often fail to achieve the level of precision, specificity, and sensitivity needed for medical diagnosis.[41]

.

Efficacy of Biomarkers in Diagnosis

Early Detection and Risk Assessment

Biomarkers hold significant importance in the preliminary identification and risk assessment of numerous health conditions, playing a pivotal role in enhancing healthcare outcomes. Biomarkers serve as valuable tools in evaluating an individual's susceptibility to cancer. They offer insights into genetic predispositions, exposure to environmental carcinogens, and other contributing factors that influence cancer development. Identifying cancer in its initial phases is crucial for improving patient survival rates. Biomarkers enable the identification of malignancies before they progress to advanced stages, thereby facilitating timely intervention and treatment. The successful implementation of early detection technologies has contributed to decreased mortality rates associated with common cancers such as colon, cervical, and breast cancers. These advancements underscore the importance of leveraging biomarkers in cancer screening and diagnosis. However, challenges persist, including the necessity for comprehensive prospective validation studies to establish the reliability and effectiveness of screening tools. Robust validation processes are essential to ensure the accuracy and clinical utility of biomarker-based screening methodologies.[42]

Biomarkers play a multifaceted role in diagnosing dementia-related conditions, monitoring responses to treatment, and tracking disease progression over time. For instance, elevated cholesterol levels serve as a biomarker indicative of an increased risk of heart attack, emphasizing the diverse applications of biomarkers beyond cancer diagnosis.[43] In the context of cancer treatment, biomarkers serve as vital indicators for monitoring therapy response and guiding clinical decision-making. Clinicians can get important insights into the efficacy of therapies through changes in biomarker levels throughout therapy. Tailoring treatment approaches based on individual biomarker profiles enhances the likelihood of treatment success and minimizes adverse effects. Certain therapies demonstrate enhanced efficacy in patients exhibiting specific biomarker signatures, highlighting the importance of personalized medicine in oncology.[4]

Predictive and Prognostic Value of Biomarkers

Biomarkers play a central role in personalized medicine, aiding both clinical decision-making and research initiatives. There is an important difference among predictive biomarkers. Analytical biomarkers, independent of therapy activities, offer evidence regarding the expected medical result, including illness development, death, or recurrence. They offer insights into a patient's health trajectory independent of specific therapies. For example, elevated levels of a particular biomarker may indicate an unfavorable prognosis, even without treatment. On the other hand, predictive biomarkers are linked to the possibility of response or non-response toward a specific treatment. They help determine whether patients are expected to profit from a particular treatment compared to their baseline condition. For instance, the presence of a specific genetic marker may forecast the patient's response to a targeted

drug treatment.[45]

Understanding the distinction between prognostic and predictive biomarkers is crucial for effective treatment planning. Accurate identification of these biomarkers informs clinicians about overall health prognosis and the potential efficacy of specific treatments. Moreover, differentiating between prognostic and predictive biomarkers helps avoid misinterpretation, which could lead to significant consequences such as financial burdens, ethical dilemmas, and personal ramifications. While prognostic biomarkers provide insights into overall health outcomes, predictive biomarkers guide treatment decisions by predicting response to specific therapies. This understanding of the differences empowers healthcare providers to tailor patient care strategies and optimize treatment effectiveness.[45]

Comparative Analysis of Biomarker Efficacy

Poly(ADP-ribose) polymerase (PARP) enzymes are important for mending single-strand break via base-excision process.[46] PARP inhibitors also known as PARPi cause increased chromosomal instability and apoptosis, with a focus on HRD cancers.[47] The therapy for ovarian cancer has changed dramatically since PARPi was introduced ten years ago. In patients who continue to respond partially or completely to platinum-based chemotherapy, PARPi indicate increase progression-free survival (PFS), a clinical endpoint commonly used in cancer medical trials and studies.[48] In the past, PARPi were used to maintain advanced disease as a second-line monotherapy. Olaparib was employed in clinical practice prior to the introduction of rucaparib and niraparib as PARPi. The efficacy of rucaparib, veliparib, niraparib, and olaparib as first-line treatment aimed at patients responding completely or partially to platinum-based chemotherapy was further demonstrated by further studies. While olaparib and niraparib have FDA clearance for first-line use, veliparib and rucaparib are currently under investigation. Consistent results indicate that individuals with BRCA mutations respond better to PARPi, with consistent hazard ratios (HRs) through trials, although changes in patient profiles, treatment regimens, as well as trial designs. Therefore, good responses to polymerase inhibitor (ADP-ribose) treatment are consistently predicted by BRCA mutations. Finding more HRD biomarkers beyond BRCA mutations is necessary, even if individuals with wild-type (wt) BRCA may potentially benefit from PARPi therapy. Furthermore, investigating "BRCAness," or synthetic lethality mechanisms similar to those seen in BRCA-mutated cancers, may increase the range of applications for PARP inhibitors. The indications for PARP inhibitor therapy may be expanded by looking into mutations in homologous recombination-related genes not implicated in the BRCA pathway, while further study is required in this area.[49,50]

Biomarkers in Treatment Strategies

A Targeted Therapies Based on Biomarker Profiles

In the management of ovarian cancer, recent therapeutic advancements like targeted therapies and immunotherapies have brought about a paradigm shift towards personalized

treatments. When taken with platinum/taxane-based chemotherapy, bevacizumab, a medication that inhibits angiogenesis, has proven to increase PFS (progression-free survival) among individuals with ovarian cancer approximately 4 months. With respect to National Comprehensive Cancer Network (NCCN) recommendation, this approach is currently used as the initial treatment.[51] A third or so of epithelial ovarian cancers have recombination homology repair deficiencies (HRDs), which make them more susceptible to PARP yet immune to platinum-based treatment. With a notable improvement in patient satisfaction, PARP inhibitors are now the norm for second-line and subsequent therapies as well as first-line maintenance therapy. Nonetheless, the key obstacle facing PARPi in medical practice is the rise in medication resilience.[52] Moreover, overall restrictive malignancy in cancer of the ovary limits the efficacy of immune check point inhibitors (ICIs), which attack Programmed cell death protein 1 and PD-L1 (Programmed cell death ligand 1) and Cytotoxic T-Lymphocyte-Associated Protein 4 as monotherapy. Compared to targeted agents, they are not as effective. Consequently, investigating ICI combinations with targeted therapy and chemotherapy is being done as a possible tactic to improve treatment results. This strategy, which offers a potential direction for further study, attempts to optimize therapeutic advantages by combining several therapy methods.[53,54]

Challenges and Opportunities in Biomarker-Guided Treatments

The potential of biomarker-guided studies to improve therapeutic benefit-risk ratios and promote drug development has garnered significant interest. These studies use biomarkers to pinpoint patient subgroups that are either more likely to benefit from a certain medication or, on the other hand, more likely to have negative side effects. Obstacles in practice: obtaining adequate financing for studies guided by biomarkers is a formidable task that demands enormous financial means. It is crucial to strike a balance between protecting patient privacy, getting informed consent, and following legal requirements.

- Finding appropriate subjects with certain biomarkers may be difficult, which might extend the duration of trials. Maintaining trial integrity requires making sure that laboratory evaluations are reliable and sample collection is accurate.
- Measurably interpreting trial results requires the validation and effective interpretation of biomarker data.
- To maximize insights and optimize resource use, collaborative activities and data sharing initiatives are essential.[55] Personalized medicine has advanced significantly in the last several years. One such stride is the use of biomarker-guided trials, which aim to provide patients with individualized therapies based on their unique requirements and features. Although biomarker-guided trials pose several problems, they have great promise to tailor therapy to the specific needs of each patient. To reach their full potential in the field of customized

medicine, they must overcome pragmatic obstacles and adopt cooperative strategies.[55]

Clinical Trials and Case Studies

In the field of gynaecological cancers, biomarkers are essential instruments that provide vital information on diagnosis, prognosis, and therapeutic approaches. The importance of these indicators can be better understood by looking at notable cases.

Analyzing Blood-Based Diagnostic Indicators in Uterine Carcinoma

Although uterine carcinoma (UC) also called endometrial cancer (EC) is the most common gynecological cancer globally, no reliable prompt screening techniques are available at this time. Researchers have examined 331 blood samples of women with EC, benign uterine lesions, breast cancer (BC), and healthy controls. To identify putative markers of EC, they evaluated a range of biomarkers.[56] Among the indicators assessed, acylcarnitines surfaced as a potentially useful option. Interestingly, malonylcarnitine showed promise in differentiating EC patients from BC patients as well as healthy controls.

Its potential as a diagnostic tool was highlighted by its levels of sensitivity and specificity. Moreover, tryptophan was identified by amino acid profile as a factor that differentiates EC from benign lesions. Its usefulness in differentiating between these situations is highlighted by its strong performance in sensitivity and specificity.[56] These blood-based indicators highlight the need for additional validation and investigation in clinical settings by providing important opportunities for the early diagnosis of EC.

Histological and Molecular Biomarkers in Endometrial Cancer

There are several histological subtypes of endometrial cancer, and each has unique therapeutic and prognostic consequences. Immunohistochemical and molecular indicators greatly enhance the thorough characterisation of this cancer by supplementing histological evaluations.[57] By combining immunohistochemistry, histology, and genetic analysis, physicians are able to comprehend endometrial cancer subtypes in a more sophisticated manner. This comprehensive strategy makes it easier to develop individualized treatment plans and make prognostic evaluations, which eventually improves patient outcomes.

Gynecological Malignancies and Tumor Markers

Although not intrinsically tumor-specific, tumor markers are essential in diagnosis and follow-up of gynecological malignancies. These markers allow for the differential identification of different forms of cancer by including a wide range of chemicals generated by malignant tumors or surrounding tissues.[58] Tumor markers provide useful information for diagnosis, but their clinical relevance goes beyond identification. They optimize patient management techniques by tracking the disease's progression, guiding therapeutic interventions, and providing information for treatment decisions. Essentially, continuous studies on gynecological cancers highlight how crucial biomarkers are to improving the precision of diagnosis, the accuracy of

prognosis, and the effectiveness of treatment. In the field of women's health, practitioners aim to improve patient outcomes and quality of life by utilizing these findings.

Ethical and Regulatory Considerations

Ethical Implications of Biomarker Testing

In the realm of gynecological malignancies, the exploration of biomarker testing raises a myriad of ethical considerations that necessitate careful examination:

- Participant Confidentiality and Privacy: The essence of biomarker research lies in the collection of samples and data from individuals battling cancer. Preserving participant confidentiality and privacy stands as a paramount ethical obligation. However, achieving a delicate balance between obtaining informed consent and maintaining efficient biobank operations poses significant challenges.
- Industry-Academia Collaborations: The synergy between industry and academia fuels biomedical progress, fostering innovations in the field. Yet, the convergence of these entities also introduces the potential for financial conflicts of interest (FCOIs), which can jeopardize the integrity of scientific endeavors.
- Ethical Issues in Cancer Screening and Diagnosis: Biomarkers provide valuable information on the course and prognosis of cancer, making them essential instruments for screening and diagnosis. But there is always the worry about overdiagnosis and the potential for overtreatment that follows, especially when it comes to molecular diagnosis. To lessen the detrimental effects of overdiagnosis on patient care and wellbeing, a thorough knowledge of the phenomenon is necessary.[58]

Ovarian Cancer Biomarkers: In spite of intensive efforts, cancer antigen 125 (CA125) remain the precise biomarker that is often employed in clinical setting to diagnose ovarian cancer. Not encode proteins, and circulating tumor DNAs are emerging as interesting options in the ongoing search for alternative markers. Still, none have been able to match CA125's effectiveness.[59] *Uterine and Cervical Cancer Biomarkers:* Investigations into biomarkers for uterine and cervical cancers are actively underway, seeking to enhance early detection and treatment efficacy. In essence, navigating the ethical terrain of biomarker development necessitates a delicate equilibrium between advancing scientific frontiers and safeguarding the well-being of research participants. It is incumbent upon researchers, clinicians, and stakeholders to uphold ethical principles in every facet of biomarker exploration and implementation.

Regulatory Framework for Biomarker Development and Validation

Creating and validating biomarkers is essential for guiding drug development plans and enabling well-informed decision-making procedures.

Guidelines on the establishment and testing of biomarkers: A conference report emphasizes the need of appropriate validation of biomarker

techniques. By validating the procedures, it is ensured that the data produced are robust, accurate, dependable, and sufficient to aid in legal processes for making decisions. "Fit-for-purpose" refers to how crucial it is to customize validation efforts to the intended application of the biomarker test and the related regulatory requirements. Maintaining accuracy and dependability may require an ongoing, iterative validation process if the intended application changes.[60] The Regulatory View from the FDA CDER representative Dr. Yow-Ming Wang stresses the significance of biomarker assay validation in order to guarantee the validity of produced data, which supports regulatory decision-making procedures. The FDA's endorsement of robust biomarker validation reflects its commitment to upholding standards of accuracy and reliability in the evaluation of drug candidates.[61]

Biomarker Qualification Programme: Recognizing the significance of biomarkers in drug development, the FDA has instituted the Biomarker Qualification Programme. The creation and regulatory approval of biomarkers meant for use in drug development projects are facilitated by this programme well-organized architecture. By establishing clear guidelines and criteria, the programme aims to streamline the validation and qualification processes, thereby expediting the integration of biomarkers into drug development programmes.[60] Regulatory agencies, such as the FDA, underscore the importance of rigorous biomarker validation processes to ensure the integrity and reliability of data generated during drug development endeavours. The establishment of programs like the Biomarker Qualification Program reflects a proactive approach to harmonizing standards and promoting consistency in biomarker evaluation. These regulatory initiatives serve as foundational pillars for fostering confidence in biomarker-driven decision-making processes, ultimately advancing the development of safe and effective therapeutics. For more comprehensive insights, the provided references can offer detailed information on regulatory guidelines and procedures.

Future Directions and Challenges

In recent decades, the field of gynecology has experienced remarkable progress driven by cutting-edge research, technological innovations, and a growing focus on patient-centered care. Minimally invasive gynecological procedures have emerged as a revolutionary advancement, offering significant advantages over traditional open surgeries. Among the most prominent techniques are laparoscopy and robotic-assisted procedures. Laparoscopy, sometimes called keyhole surgery or minimally invasive surgery, is a surgical procedure in which the pelvic organs are accessed and visualized by inserting a thin, lit tube (called a laparoscope) via tiny abdominal wall incisions. Laparoscopic operations have a number of advantages over open surgeries which include less discomfort, less hospital admission, quicker recovery time, and improved cosmetic outcomes with less scarring. These benefits lead to lower medical expenses and more patient satisfaction.[62,63]

.

Robotic-assisted procedures represent another evolution in minimally invasive surgery. With the increased accuracy and three-dimensional visibility that robotic systems provide, surgeons can execute intricate surgeries with better results.[64] The advanced capabilities of robotic platforms allow for greater range of motion, precise tissue manipulation, and reduced surgeon fatigue, all of which contribute to better patient results. Consequently, robotic-assisted surgeries have become increasingly popular in gynecology, particularly for procedures such as hysterectomy and myomectomy. Comparative studies between robotic-assisted laparoscopic surgery and conventional laparoscopy have demonstrated comparable outcomes, with robotic surgery exhibiting advantages in areas such as reduced blood loss and shorter hospital stays.[65,66]

The bio-processing method is a revolutionary development in healthcare, precision medicine is an emerging paradigm in gynecology that attempts to give individualized and customized treatment plans for each patient. With this method, doctors may give personalized therapies with enhanced therapeutic outcomes and fewer side effects by better understanding the exceptional features of patient's condition through the use of advances in genetics, molecular biology, and biomarker analysis. In addition to genetic and molecular profiling, biomarker profiling offers important details about certain bio-molecules that signify the existence, prognosis, or response to therapy of a disease. Serum CA-125 levels have long been employed in therapy of cancer of the ovary toward treatment response and identify disease recurrence.[43] In addition to CA-125, emerging biomarkers such as ROMA (Risk of Ovarian Malignancy Algorithm) have demonstrated promise in enhancing ovarian cancer diagnosis and risk assessment.[67] Substantial development has been made in the field of reproductive medicine, especially with regard to assisted reproductive technologies (ART), which provide hope and solutions to infertile couples. The most revolutionary of these discoveries is *in vitro* fertilization (IVF), which has transformed the treatment of several infertility-related conditions and allowed millions of couples to fulfill their ambition of becoming parents.[68] The method of fertilizing sex cells outside of the woman's body in a controlled laboratory environment is known as in vitro fertilization, or IVF. Success rates have increased dramatically over time because of advancements in IVF methods, culture medium, and laboratory techniques.[69]

The advent of telemedicine, smartphone apps, and digital health technologies has revolutionized the healthcare environment in recent years. Since digital technologies are increasingly being used to improve patient care, increase access, and maximize clinical results, gynecology, as a specialty medical field, has not been immune to these changes. By examining how these technologies are transforming patient-provider relationships and enhancing overall healthcare delivery, this subtopic seeks to understand the function and significance of digital health and telemedicine in gynecological care. The creation of mobile applications specifically suited to the health requirements of women is among the most important contributions of digital health to the

field of gynecology. Numerous functions are available in mobile applications, such as fertility tracking, menstrual cycle tracking, reminders for contraceptives, and reproductive health education materials.[70] With the help of these applications, women can easily monitor key health indicators such as ovulation and menstrual cycles, giving them greater control over their health. Furthermore, fertility awareness-based strategies have been made easier by mobile applications, which give women precise and customized information to help with family planning.[71]

These availability of evidence-based information on these applications encourages women to actively participate in their healthcare decisions and helps them make well-informed decisions. Furthermore, telemedicine has shown to be a game-changer for gynecological treatment, particularly in rural and disadvantaged areas. By using technology to facilitate remote consultations between patients and medical professionals, telemedicine helps patients receive specialist treatment more easily and transcends geographic boundaries.[71]

Telemedicine provides a lifeline for women who are geographically confined or have limited access to gynecological treatments by allowing them to connect with knowledgeable doctors wherever they may be. This is especially important when it comes to maternity and reproductive healthcare, since prompt access to treatment might be essential to achieving successful results. Clinical efficacy of telemedicine consultations for surgical follow-ups, family planning counseling, and prenatal care has been shown to be on a par with in-person visits.[72]

The extensive use of telemedicine and digital health in gynecological care is nevertheless fraught with difficulties, notwithstanding these encouraging developments. Concerns about data security and privacy, regulatory compliance, and unequal access to digital technology are important issues that need to be taken into consideration. When implementing digital health solutions, it is crucial to ensure patient confidentiality and data protection. Furthermore, in order to prevent escalating already-existing healthcare inequalities, fair access to digital tools and telemedicine services is essential.

Addressing Limitations and Unmet Needs

To effectively implement patient-centered care and shared decision making in gynecology, one must be willing to engage in collaborative patient engagement and have strong communication skills. In order to help patients feel comfortable communicating their concerns and desires, healthcare practitioners should work to provide a compassionate and supportive environment.[72]

Using written materials and visual aids in the decision-making process can help patients better comprehend their treatment options and participate in the process. Furthermore, it is critical to foster cultural competency and awareness of the many patient backgrounds in order to effectively meet the unique needs and perspectives of women from other groups.

Summary of Key Findings

the paper emphasizes the importance of biomarkers in the treatment and screening of

gynecological cancers with an emphasis on their functions in early identification, risk evaluation, and treatment response monitoring. Biomarkers serve as detection parameter of biological procedures or conditions within the body, and in the context of gynecological cancers, this marker play a vital role in guiding clinical decisions. There are several types of biomarkers discussed, each serving different functions in healthcare. Prognostic biomarkers offer insights into the probable trajectory of the illness, predictive biomarkers forecast individual response toward specific diagnosis, pharmacodynamic biomarkers evaluate the impact of a medication on its target, and surrogate endpoint biomarkers function as stand-ins for clinically significant endpoints in clinical trials. Despite the advancements made in the field, challenges persist in ensuring the efficacy of biomarkers, particularly in early detection. Detailed validation procedures are obligatory to prove the validity and dependability of biomarkers, guaranteeing their efficacy in supporting the early detection and management of gynecological cancers. These innovative approaches have transformed the management of ovarian cancer, emphasizing the shift towards personalized medicine where each patient's unique qualities are taken into account when designing their treatment.

Biomarkers hold immense potential in enhancing the accuracy and efficiency of diagnosing gynecological cancers. By identifying specific molecular signatures or biological markers associated with these malignancies, clinicians can potentially detect them at earlier stages when treatment options may be more effective. Biomarker-driven diagnostic approaches have the potential to streamline the diagnostic process, reduce the need for invasive procedures, and improve overall patient outcomes. One of the most significant implications of biomarker research in gynecological malignancies is the prospect of personalized treatment strategies. Biomarker profiles can provide important information on the molecular features of cancers, allowing medical professionals to customize therapy regimens for specific patients. Through recognizing biomarkers that indicate responsiveness to specific therapies, healthcare providers can optimize treatment selection, potentially enhancing treatment efficacy while minimizing adverse effects. Biomarkers also hold prognostic value by providing critical information about disease progression and patient outcomes. By analyzing biomarker profiles, clinicians can assess the aggressiveness of a tumour, predict the likelihood of recurrence, and anticipate patient survival rates. This prognostic information is invaluable for informing treatment decisions, facilitating discussions about prognosis with patients, and guiding long-term management strategies. The review underscores the importance of ongoing research into novel biomarkers and their integration into clinical practice. As the insight into the molecular mechanisms underlying gynecological cancers continues to evolve, there is a pressing need to identify new biomarkers that can further refine diagnostic accuracy, treatment selection, and prognostic assessment. Future research endeavours may

focus on elucidating the complex interplay between biomarkers, tumour biology, and patient outcomes, ultimately paving the way for more personalized and effective approaches to gynecological cancer care. The implications of biomarker research in gynecological malignancies are far-reaching, offering opportunities to enhance diagnosis, personalize treatment approaches, provide prognostic insights, and drive future research efforts aimed at improving patient outcomes. These findings underscore the importance of continued collaboration between clinicians, researchers, and other stakeholders to harness the full potential of biomarkers in the fight against gynecological cancers.

CONCLUSION

Biomarkers are crucial in the treatment and screening of gynecological cancers, offering insights for early identification, risk evaluation, and monitoring treatment responses. They can guide clinical decisions by providing prognostic, predictive, pharmacodynamic, and surrogate endpoint information. Despite advancements, challenges in validating these biomarkers for early detection persist. Continued research is essential to enhance diagnostic accuracy, personalize treatments, and improve patient outcomes. The integration of novel biomarkers into clinical practice will further refine diagnostic processes, treatment selection, and prognostic assessments, emphasizing the shift towards personalized medicine.

REFERENCES

1. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circul*. 2006; 113:2335–2362.
2. Biomarkers Defnitions Working Group. Biomarkers and surrogate endpoints: preferred defnitions and conceptual framework. *Clin Pharmacol Ther*. 2001; 69:89–95.
3. International Programme on Chemical Safety. Biomarkers in risk assessment: validity and validation. World Health Organization, Geneva, 2001.
4. Sölétormos G, Duffy MJ, Hassan SOA, et al. Clinical use of cancer biomarkers in epithelial ovarian cancer: updated guidelines from the European group on tumor markers (EGTM). *Int J Gynecol Cancer*. 2016; 26:43-51.
5. Muinao T, Deka Boruah HP, Pal M. Diagnostic and Prognostic Biomarkers in ovarian cancer and the potential roles of cancer stem cells - An updated review. *Exp Cell Res.* 2018; 362:1-10.
6. Yang WL, Lu Z, Bast RC Jr. The role of biomarkers in the management of epithelial ovarian cancer. *Expert Rev Mol Diagn.* 2017; 17:577-591.
7. Guo N, Peng Z. Does serum CA125 have clinical value for follow-up monitoring of postoperative patients with epithelial ovarian cancer? Results of a 12-year study. *J Ovarian Res.* 2017; 10:14.
8. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer

Linkage Consortium. *Lancet*. 1994; 343:692–695.

9. National Cancer Institute Dictionary of Cancer Terms https ://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed 7 Sept., 2020.
10. Chiyoda T, Dozen A, Saotome K, Nanki Y, Aoki D. In: Shimada H (eds), Biomarkers of gynecological cancers. Biomarkers in Cancer Therapy: Liquid Biopsy Comes of Age. 2019. Pp. 133-150.
11. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterol*. 1999; 116:1453–1456.
12. Mathews J, Amaravadi L, Eck S, Stevenson L, Wang YM, Devanarayan V, et al. Best practices for the development and ftfor-purpose validation of biomarker methods: a conference report. *AAPS Open*. 2022; 8:2.
13. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative group on hereditary non-polyposis colorectal cancer (ICG-HNPCC). *Dis Colon Rectum*. 1991; 34:424–425.
14. Edwards P, Monahan KJ. Diagnosis and management of Lynch syndrome. *Frontline Gastroenterol*. 2022; 13(e1):e80-e87.
15. Clark SK. Management of genetically determined colorectal cancer. *Surgeon*. 2019; 17(3):165–171.
16. Mai PL, Malkin D, Garber JE, et al. Li-Fraumeni syndrome: report of a clinical research workshop and creation of a research consortium. *Cancer Genet*. 2012; 205:479–487
17. Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG clinical guidelines: colorectal cancer screening 2021. *Am J Gastroenterol Suppl*. 2021; 116(3):458–479.
18. Sanchez-Mete L, Stigliano V. Update on small bowel surveillance in hereditary colorectal cancer syndromes. *Tumori*. 2019; 105(1):12–21.
19. Varley JM. Germline TP53 mutations and Li-Fraumeni syndrome. *Hum Mutat*. 2003; 21:313–313
20. Ji M, Wang L, Shao Y. A novel dysfunctional germline P53 mutation identified in a family with Li-Fraumeni syndrome. *Am J Cancer Res*. 2018; 8:165–169.
21. Schneider K, Zelley K, Nichols KE, Garber J. Li-Fraumeni syndrome. In: Adam M, Ardinger H, Pagon R, et al., eds. GeneReviews. www.ncbi.nlm.nih.gov/books/. Published January 19, 1999. Updated April 11, 2013. Accessed January 1, 2020.
22. Ponikowski P, Voors AA, Anker SD et al ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail*. 2016; 18:891–975.

23. Biomarkers Defnitions Working Group. Biomarkers and surrogate endpoints: preferred defnitions and conceptual framework. *Clin Pharmacol Ther*. 2001; 69:89–95.
24. Zamwar UM, Anjankar AP. Aetiology, Epidemiology, Histopathology, Classification, Detailed Evaluation, and Treatment of Ovarian Cancer. *Cureus*. 2022; 14:e30561.
25. Shastri SS, Temin S, Almonte M, Basu P, Campos NG, Gravitt PE, et al. Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Guideline Update. *JCO Global Oncol*. 2022; 8:e2200217.
26. Monti M, D'Aniello D, Scopelliti A, Tibaldi V, Santangelo G, Colagiovanni V, et al. Relationship between cervical excisional treatment for cervical intraepithelial neoplasia and obstetrical outcome. Minerva Obstetrics and Gynecology. 2021; 73:233-246.
27. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. The New Engl J Med. 2022; 386:437–448.
28. Zamwar UM, Anjankar AP. Aetiology, Epidemiology, Histopathology, Classification, Detailed Evaluation, and Treatment of Ovarian Cancer. *Cureus*. 2022; 14:e30561.
29. Kim SI, Kim JW. Role of surgery and hyperthermic intraperitoneal chemotherapy in ovarian cancer. ESMO Open. 2021; 6:100149.
30. Verbakel JY, Heremans R, Wynants L, Epstein E, De Cock B, Pascual MA, et al. Risk assessment for endometrial cancer in women with abnormal vaginal bleeding: Results from the prospective IETA-1 cohort study. *Int J Gynaecol Obstet*. 2022; 159: 103–110.
31. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res*. 2019; 12:28.
32. Kim BG. Squamous cell carcinoma antigen in cervical cancer and beyond. *J Gynecol Oncol.* 2013; 24(4):291.
33. Güzel C, van Sten-Van't Hoff J, de Kok IMCM, et al. Molecular markers for cervical cancer screening. *Exp Rev Proteomics.* 2021; 18(8):675-691.
34. Miao M, Miao Y, Zhu Y, Wang J, Zhou H. "Advances in Exosomes as Diagnostic and Therapeutic Biomarkers for Gynaecological Malignancies." *Cancers.* 2022; 14(19):4743.
35. Carser JE, Quinn JE, Michie CO, O'Brien EJ, McCluggage WG, Maxwell P, Lamers E, Lioe TF, Williams AR, Kennedy RD, Gourley C, Harkin DP. BRCA1 is both a prognostic and predictive biomarker of response to chemotherapy in sporadic epithelial ovarian cancer. *Gynecol Oncol*. 2011; 123(3):492-498.
36. Kaplan JM, Wong HR. Biomarker discovery and development in pediatric critical care medicine. *Pediatr Crit Care Med*. 2011; 12(2):165-173.

37. Robinson WH, Lindstrom TM, Cheung RK, Sokolove J. Mechanistic biomarkers for clinical decision making in rheumatic diseases. *Nat Rev Rheumatol*. 2013; 9(5):267-276.
38. Seo Y, Park YH, Ahn JS, et al. *PIK3CA* Mutations and Neoadjuvant Therapy Outcome in Patients with Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: A Sequential Analysis. *J Breast Cancer*. 2018; 21(4):382-390.
39. Yang J, Nie J, Ma X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Mol Cancer.* 2019; 18:26.
40. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Int Med*. 1996; 125(7):605-13.
41. Nimse SB, Sonawane MD, Song KS, Kim T. Biomarker detection technologies and future directions. *Analyst*. 2016; 141(3):740-755.
42. Brenner DE, Normolle DP. Biomarkers for cancer risk, early detection, and prognosis: the validation conundrum. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(10):1918-1920.
43. Ahmed RM, Paterson RW, Warren JD, Zetterberg H, O'brien JT, Fox NC, Halliday GM, Schott JM. Biomarkers in dementia: clinical utility and new directions. *J Neurol Neurosurg Psychiatry*. 2014; 85(12):1426-1434.
44. Lim C, Tsao MS, Le LW, Shepherd FA, Feld R, Burkes RL, Liu G, Kamel-Reid S, Hwang D, Tanguay J, da Cunha Santos G. Biomarker testing and time to treatment decision in patients with advanced nonsmall-cell lung cancer. *Ann Oncol*. 2015; 1;26(7):1415-21.
45. Zhu W, Lévy-Leduc C, Ternès N. Identification of prognostic and predictive biomarkers in high-dimensional data with PPLasso. *BMC Bioinformatics*. 2023; 23; 24(1):25.
46. De Lorenzo SB, Patel AG, Hurley RM, et al. The Elephant and the Blind Men: Making Sense of PARP Inhibitors in Homologous Recombination Deficient Tumor Cells. *Front Oncol*. 2013; 3:228.
47. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005; 434:917-921.
48. Ledermann J, Harter P, Gourley C. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014; 15:852-861.
49. Armstrong DK, Alvarez RD, Bakkum-Gamez JN. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:191-226.
50. Shah S, Cheung A, Kutka M. Epithelial Ovarian Cancer: Providing Evidence of Predisposition Genes. *Int J Environ Res Pub Health*. 2022; 19:8113.
51. Armstrong DK, Alvarez RD, Backes FJ, Bakkum-Gamez JN, Barroilhet L, Behbakht K. NCCN Guidelines® insights: Ovarian cancer, version 3.2022.

J Natl Compr Canc Netw. 2022; 20(9):972–980.

52. Miller RE, Leary A, Scott CL, Lord CJ, Bowtell D, Chang DK. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol*. 2020; 31(12):1606–1622.
53. Li H, Liu ZY, Wu N., Chen YC, Cheng Q, Wang J. PARP inhibitor resistance: The underlying mechanisms and clinical implications. *Mol Cancer*. 2020; 19(1):107.
54. Yang C, Xia BR, Zhang ZC, Zhang YJ, Lou G, Jin WL. Immunotherapy for ovarian cancer: Adjuvant, combination, and neoadjuvant. *Front. Immunol.* 2020; 11:577869.
55. Antoniou M, Kolamunnage-Dona R, Wason J, Bathia R, Billingham C, Bliss JM, Brown LC, Gillman A, Paul J, Jorgensen AL. Biomarker-guided trials: challenges in practice. *Contemp Clin Trials Commun*. 2019; 16:100493.
56. Schuhn A, Tobar TW, Gahlawat AW, Hauke J, Baumann L, Okun JG, Nees J. Potential of blood-based biomarker approaches in endometrium and breast cancer: a case-control comparison study. *Arch Gynecol Obstet*. 2022; 306(5):1623-1632.
57. Zannoni GF, Bragantini E, Castiglione F, Fassan M, Troncone G, Inzani F, Pesci A, Santoro A, Fraggetta F. Current prognostic and predictive biomarkers for endometrial cancer in clinical practice: Recommendations/proposal from the Italian study group. *Front Oncol*. 2022; 12:805613.
58. Chiyoda T, Dozen A, Saotome K, Nanki Y, Aoki D. Biomarkers of gynecological cancers. Biomarkers in Cancer Therapy: Liquid Biopsy Comes of Age. 2019:133-150.
59. Mathews J, Amaravadi L, Eck S, Stevenson L, Wang YM, Devanarayan V, Allinson J, Lundsten K, Gunsior M, Ni YG, Pepin MO. Best practices for the development and fit-for-purpose validation of biomarker methods: a conference report. *AAPS Open*. 2022; 8(1):2.
60. Wang YC, Strauss DG, Huang SM. Use of pharmacodynamic/response biomarkers for therapeutic biologics regulatory submissions. *Biomark Med*. 2019; 13(10):805–809.
61. Clark TJ, Middleton LJ, Cooper NA. A randomised controlled trial of laparoscopic uterosacral nerve ablation for women with chronic pelvic pain. *BMJ Open*. 2015; 5:e006408.
62. Sarlos D, Kots L, Stevanovic N, Schaer G. Robotic compared with conventional laparoscopic hysterectomy: a randomized controlled trial. *Obstet Gynecol*. 2012; 120:604-611.
63. Payne TN, Dauterive FR. A comparison of total laparoscopic hysterectomy to robotically assisted hysterectomy: surgical outcomes in a community practice. *J Minim Invasive Gynecol*. 2008; 15:286-291.
64. Holloway RW, Patel SD, Ahmad S, Robichaux AG, Goravanchi F, et al.

Robotically assisted gynecologic surgery in the obese patient. *Am J Obstet Gynecol*. 2009; 200:613.e1-613.e4.

65. Moore RG, Miller MC, Eklund EE. Serum levels of the ovarian cancer biomarker HE4 are decreased in pregnancy and increase with age. *Am J Obstet Gynecol*. 2012; 206:349.e1-349.e7.
66. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet*. 1978; 2:366.
67. Aungst TD. Medical applications for pharmacists using mobile devices. *Ann Pharmacother*. 2013; 47:1088-1095.
68. Freis A, Freundl-Schütt T, Wallwiener LM, Wallwiener CW, Wallwiener D. Bioinformatics support for the fertility awareness-based methods in avoiding pregnancy. *Reprod Biomed Online*. 2017; 35:308-316.
69. Ong MS, Magrabi F, Post J, Morris S, Westbrook JI. Use of clinical decision support to improve primary care identifies targets for improvement in the outpatient referral process. *J Am Med Inform Assoc*. 2016; 23:609-615.
70. Silverstein W, Lass E, Bornstein T. A randomized clinical trial of a telemedicine intervention for child disruptive behavior disorders: III. Maintenance and generalization of effects. *J Abnorm Child Psychol*. 2018; 46:1285-1298.
71. Wac K, Wac K, Prakoonwit S, Widya I, Jara AJ. Mobile healthcare and resource-constrained communities: a case study from Thailand. *J Med Syst*. 2012; 36:1437-1451.
72. Henselmans I, van Laarhoven HW, van der Vloodt J, Tokat M, Engelhardt EG. Shared decision making about palliative chemotherapy: A qualitative observation of talk about patients' preferences. *Palliat Med*. 2015; 29:261-269.